UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,356	06/03/2005	Klaus Dietzel	26794U	2653

34375 7590 10/04/2007

NATH & ASSOCIATES PLLC
112 South West Street
Alexandria, VA 22314

EXAMINER	
HOUGHTLING, RICHARD A	
ART UNIT	PAPER NUMBER
1609	

MAIL DATE	DELIVERY MODE
10/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,356	DIETZEL ET AL.	
	Examiner	Art Unit	
	Richard A. Houghtling, Ph.D.	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :06 September 2005 and 13 March 2006.

DETAILED ACTION

1. **Under Rule 1.126, the second occurrence of claim 5 is, now claim 6 and subsequent claims are renumbered, thus the claims are 1-24.**

2. Claims 1-24 are pending in the application received 03 June 2005; receipt of a Preliminary Amendment also filed 03 June 2005 is acknowledged. Applicants' preliminary amendment to the claims Applicants' requests are entered into the record, and are examined on their merits, herein.

Foreign Priority

3. Applicants' claim to foreign priority under 35 U.S.C. 119(a)-(d) is acknowledged; a certified copy was filed 03 June 2005.

Information Disclosure Statements

4. Acknowledgement of receipt of two information disclosure statements filed by applicants on 06 September 2005 and 12 March 2006; examiner entered disclosures into the record and references were considered.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-6 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Keller et al. (US Patent 6,645,466).

Applicants' invention is drawn to a pharmaceutical composition comprising ciclesonide and formoterol, which may be in a fixed or free combination (claim 1), including pharmaceutically acceptable excipients or vehicle suitable for inhalation using a powder inhaler (claim 2). The pharmaceutical composition of claim 2 is further limited by dependent claims 3-6, wherein, the composition is fixed, ready-mixed dosage (claim 3), includes lactose as an excipient (claim 4); or a free combination wherein, each drug is provided as separate pack units for successive (claim 5) or sequential (clam 6) administration.

Keller et al. teaches dry powdered formulations for inhalation, which have improved moisture resistance, and in particular correspond to preparations comprising one or more active compounds, such as formoterol (col. 6, line 16) and ciclesonide (col. 6, line 21) and magnesium stearate. Both formoterol and ciclesonide possess chiral carbons, and Keller et al. further teaches that optical isomers or diastereoisomeric mixtures of racemate are also well within the scope of dry-powdered formulations that can be improved (col. 6, lines 33-37). Preparation of these formulations may result from mixing pharmaceutically active compositions together or separately in any desired sequence (col. 8, lines 53-59); thus accommodating for whether the drug was ready-mixed in a fixed combination or available separately (ie. blister packs, see col. 1, lines 44-52).

Furthermore, the Keller et al. composition anticipates the instantly claimed pharmaceutical composition comprising solvates, epimers or salts of ciclesonide and R,R-formoterol. Most notably, is the inclusion of a list of acids that may be used to prepare R,R-formoterol salts (see col. 6, lines 41-51), as well as, inclusion of salts of hydrates as found for formoterol in Tables 1-3 (see col. 10, lines 15-35; col. 11, lines 1-20; col. 11, lines 46-63); with particular emphasis on formoterol fumarate or tartrate and formoterol fumarate dihydrate. Therefore, applicants' claims drawn to a composition comprising the R-epimer of ciclesonide or R,R-formoterol are well within the scope of the Keller et al. composition. In summary, the improved dry-powdered pharmaceutical

composition taught by Keller et al. clearly anticipates applicants' claimed pharmaceutical claim 1 of claims 2-6 compositions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-10, 18-20 rejected under 35 U.S.C. 103(a) as being unpatentable over Keller et al. as applied to claims 1-6 above, and further in view of Postma et al. (2001, reference V).

Applicants' claimed pharmaceutical composition drawn by independent claim 2 which is further limited by claims 7-10 comprises the R-epimer of ciclesonide (greater than 95%, claim 7) and R,R-formoterol formulated as a hydrate, salt, or hydrate of a salt thereof (claim 8), which salts are prepared by reaction with any of the acids listed (claim 9), which acid is further limited to tartaric acid or fumaric acid (claim 10). Likewise, applicants' also claim a separate pharmaceutical composition drawn by claims 2-3 comprising, R-epimer of ciclesonide (>95%, claim 18) and a salt of R,R-formoterol determined by its reaction with acid (listed in claim 19), which is further restricted to tartaric acid.or fumaric acid (claim 20).

Keller et al. is relied upon for the pharmaceutical composition described above which teaches dry powdered formulations for inhalation, including a composition combining formoterol and ciclesonide. Keller et al. teaches that active pharmaceuticals, including those compounds, which possess chiral centers as epimers or racemates may

also be improved, however, a specific limitation as to the purity of the chiral species is not described.

Postma et al. (2001) reports findings of a clinical study that teaches utility and efficacy of ciclesonide in asthma patients via a single dosing regimen using a powder inhaler and selection of the R-epimer of ciclesonide for further clinical development. This clinical study found a significant treatment effect using ciclesonide (200 μg) administered once daily to patients with mild to moderate asthma symptoms (see p. 1087, Discussion, 1st ¶, lines 1-5 and 4th ¶, lines 20-22).

Ciclesonide has no biological activity until it is cleaved by an esterase, which liberates its active compound which then binds to the glucocorticoid receptor (p. 1083, 2nd ¶, lines 1-2 and 7-9). Additionally,

> "Ciclesonide which has a chiral centre in the acetal side chain, exists as two epimers with different receptor affinities and metabolization rates. **Only** R-ciclesonide was selected for clinical development," (see p. 1083, 2nd ¶, lines 2-6).

Thus, R-ciclesonide was developed because it possessed both pharmacokinetic and pharmacodynamic properties consistent with clinical benefit. Though Postma et al. teaches the utility of ciclesonide for an airway disease such as asthma, it does not teach the combination of ciclesonide and formoterol.

Taken together, the pharmaceutical composition taught by Keller et al. comprising formoterol, ciclesonide, and magnesium stearate meets the applicants'

claimed dry-powdered compositions (claim 1, claims 2-10 or claims 2-3, 7-10 or claims 2-3, 18-20). Applicants' claims limiting ciclesonide to the R-epimer at >95% are *prima facie* obvious to one of ordinary skill in the art because Postma et al. teaches that the clinically relevant epimer is R-ciclesonide; thus, if one of ordinary skill in the art was formulating the combination found in Keller et al., it would have been prima facie obvious to use the R-epimer of ciclesonide at >95% based on the teachings of Postma et al. considering the fact that R-ciclesonide had clinical benefit to patients undergoing treatment for an airway disease, such as asthma.

7. Claims 11-17, and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Postma et al. (2001, see Ref. Y) or Taylor et al. (1999, see Ref. U) in combination with Akpinarh et al. (1999, see Ref. X) or Maesen et al. (1999, see Ref. W).

Applicants' invention further claims methods of treating airway diseases to a patient in need thereof comprising a therapeutically effective amount of ciclesonide and R,R-formoterol (claim 11), which is further limited to fixed combination compounds formulated for inhalation (claim 12) or those that includes the R-epimer ciclesonide at greater than 95% (claim 13).

Applicants' methods also include use of claimed pharmaceutical compositions. Method claims 14-17 use therapeutically effective amounts of claim 2 compositions

administered by powder inhaler to treat airway diseases (claim 14), wherein the disease is limited to obstructive bronchitis, COPD (chronic obstructive pulmonary disease), spastic bronchitis, allergic bronchitis, allergic asthma, and bronchial asthma (claim 15), and claim 16 further limits the dose ranges of ciclesonide and R,R-formoterol to 0.05-1 mg/day and 10-50 μg/day, respectively; whereas claim 17 limits the frequency of dosing to once a day. Likewise the method of claim 21 comprises a therapeutically effective amount of the pharmaceutical compositions described by claims 2-3, 7-10 or claims 2-3, 18-20 for treatment of airway diseases in a patient in need thereof.

Postma et al. is relied upon for its teachings of the clinical benefit observed for ciclesonide in the treatment of an airway disease such as asthma (see section No. 6). Although the data are convincing, Postma et al. does not teach the combination of ciclesonide and formoterol. See also above.

Taylor et al. also teaches efficacy of the corticosteroid, ciclesonide to reduce airway inflammation associated with mild to moderate asthma symptoms. Exposure of an asthmatic patient to an allergen to which he/she is sensitized results in reduced airflow via increased airway inflammation (p. 237, col. 2, 3rd ¶, lines 1-2). Using an experimental allergen (AMP bronchoprovocation), responses to allergen exposure were measured before and after 2 weeks of twice daily, inhalation of ciclesonide (50, 200, 800 or 100, 400 and 1600 μg daily; see p. 239, Fig. 1 and Table 3). Overall, the treatment of allergic asthma was well tolerated and demonstrated beneficial effects

resulting in reduced airway inflammation at low/moderate and high doses of treatment (p. 242, col. 1, lines 43-50). Furthermore, efficacy of ciclesonide treatment of asthmatics is comparable to that of budesonide, a well characterized and established inhaled steroid (p. 242, col. 2, lines 41- 47). Taylor et al. describes a method of treating allergic asthma using ciclesonide.

Maesen et al. teaches the use of inhaled formoterol to significantly reduce airway resistance and work of breathing in patients suffering from the airway disease—chronic obstructive pulmonary disease (COPD). Using once a day dosing, significant reduction in airway resistance and a significant improvement in the work of breathing are reported (see p. 1005, Table 2, 2nd ¶ entire, p. 1106, Fig. 2 and p. 1107, Fig. 3 and lines 20-27). Although, no alteration or improvement was found in the inflammatory response to formoterol, this study taught the importance of bronchodilating drugs (i.e. formoterol) as a keystone of the pharmacological therapy in dyspnoeic patients suffering from COPD (p.1107, 3rd ¶, lines 1-2).

Akpinarh et al. also teaches use of inhaled formoterol to treat airway disease in children. Distinct from Maesen et al., the asthmatic children were not restricted from regular steroid use during the clinical trial for formoterol treatment (12 μg; twice daily), thus this study effectively assessed both use of a steroid and formoterol. This treatment regimen demonstrated improved clinical symptoms and/or pulmonary function in these patients (p.45, abstract and p. 47, Discussion, col.2, 1st ¶, lines 24-26). Overall, the

authors concluded, "further adding formoterol to inhaled corticosteroids is an effective treatment option in children who are symptomatic despite regular use of inhaled corticosteroids," (p. 48, col. 1, lines 9-13). The method of Akpinarh thus teaches the utility of formoterol and corticosteroids in the treatment of airway disease—symptomatic asthma refractive to corticosteroid therapy alone; however, fails short because it does not specify ciclesonide as a possible corticosteroid to combine treatment.

Claims 11-13 are drawn to a method of treating airway diseases comprising the combination of ciclesonide and R,R-formoterol. As discussed above, Postma et al. and Taylor et al. (ciclesonide) and Maesen et al. and Akpinarh et al. (formoterol) demonstrate that each drug independently provides clinical benefit to patients suffering from bronchial asthma, allergic asthma or COPD; and further Postma et al. states that the R-epimer of ciclesonide was selected for clinical development indicating that the S-epimer does not likely share the pharmacokinetic/pharmacodynamic properties and hence marketability. Thus, the methods of claims 11 and 13 are met by combination of the teachings described above, whereas, ready-fixed combinations of the two drugs (claim 12) is an adjustment of a particular conventional working conditions (e.g., determining result effective amounts of the ingredients beneficially taught by the cited references, especially within the broad ranges instantly claimed), as well as treating a particular type of airway disease, is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan. Accordingly,

this type of modification would have been well within the purview of the skilled artisan and no more than an effort to optimize results.

Finally, claims 14-17, 21-24 are drawn to methods of treating airway diseases comprising administration by inhalation of dry-powdered pharmaceutical compositions discussed above. The methods of claims 14 or 21 to treat airway diseases comprising ciclesonide and formoterol is obvious to one of ordinary skill in the art considering each drug independently is described having efficacy in clinical studies describing similar patient populations (i.e. asthmatics). Likewise, of the four literature articles, three of the specific diseases listed in claims 15 or 22 (bronchial asthma, allergic asthma and C.O.P.D.) are represented; while, claims 16 or 23 and 17 or 24 limits the amount of drug and frequency of administration, both ciclesonide doses of 50 μg, 200 μg and 800 μg (Taylor et al.) or formoterol doses of 6 μg or 24 μg (Maesen et al.) are within the ranges claimed and each administers the drug once daily. Thus when taken together the methods used for treatment of airway diseases by administration of a composition of ciclesonide and formoterol are quite similar to those of the pending claims 14-17 and 21.

Both ciclesonide and formoterol are drugs that are known in the prior art to treat airway diseases as is illustrated by Postma et al. and Taylor et al. These clinical studies demonstrate the efficacy of ciclesonide for treatment of bronchial asthma or allergic asthma, respectively. Furthermore, each is relied upon for doses of drug administered or frequency of administration. Likewise, Akpinarh et al. and Maesen et al. teach the

efficacy of formoterol for treatment of COPD or bronchial asthma, respectively. Again, each is relied upon for drug doses or frequency of administration. Because both ciclesonide and formoterol are known to each have beneficial efficacy in treatment of airway diseases—allergic or bronchial asthma and COPD, it is *prima facie* obvious to one of ordinary skill in the art to combine these two teachings with the result being that of the compositions and/or methods of applicants' claims 1-24. The basis for this *prima facie* obviousness rejection can be found in the following case law:

> "It is however, *prima facie* obvious to combine two compositions taught in the prior art useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069,1072 (CCPA 1980).

Conclusion

In conclusion, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard A. Houghtling, Ph.D. whose telephone number is 571-272-9334. The examiner can normally be reached Monday to Thursday from 8:00 am - 5:00 pm. The examiner can also be reached on alternate Fridays.

The Group 1600 fax phone number where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on 571-272-0911.

Richard A. Houghtling, Ph.D.

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER